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(54) Use of prostaglandin D2-active substances in the treatment of ocular hypertension and glaucoma.

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US-A- 4 033 989

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Description

The present invention relates to the use of prostaglandin D_2-active substances for amelioration ocular hypertension and treating glaucoma. More particularly, the present invention provides a medicament containing a prostaglandin D_2-acting substance as an active ingredient and a method of treating ocular hypertension and glaucoma.

Glaucoma is an eye disease which is characterized by an increase of intraocular pressure. The increase of the pressure is caused by either a decreased aqueous outflow through Schlemm's canal or an abnormally increased secretion of aqueous humor. The mechanism for onset of glaucoma has not yet been sufficiently clarified. Conventional therapy comprises administration of pilocarpin, epinephrine or of adrenergic beta-blockers. However, continuous use of adrenergic beta-blockersresults in weakening their action. In severe cases, surgical operations have been often conducted to decrease intraocular pressure. It is also known that among prostaglandin(PC)s, prostaglandins D_3, E_1, E_2, E_3, $F_{2\alpha}$ and $F_{2\alpha}$ derivatives show the activity of reducing intraocular pressure. (Chiryo 68, 1207-1213 (1986), Invest. Ophthalmol. Vis. Sci. Vol.22, p.588 (1982), 26, 1178-1182 (1985), Exp. Eye Res. 38, 181-194 (1984) and USP 4599353). Some of these prostaglandins, however, have a tendency to cause inflammational reactions. Furthermore, E and F type PGs incur a transient rise in intraocular pressure (IOP) before IOP reduction when administered in higher dose, which may aggravate the disease condition. Therefore, these PGS cannot be said to be appropriate for treatment of glaucoma.

In the course of the study on the pharmacological activity of prostaglandin D_2-active substances,the present inventors have found that prostaglandin D_2-active substancescan reduce the IOP without being accompanied by the transient rise in IOP.

The action of PGD_2 per se on IOP has been reproted in the two articles. In the first article(Invest. Ophthalmol. Vis Sci. 23, 383-392, 1982), it was reported that PGD_2 showed IOP raising activity in rabbits. In the second article (Exp. Eye Res. 38, 181-194, 1984, corresponding to USP 4599353) which deals mainly with $PGF_{2\alpha}$ and its derivatives, PGD_2 was administered to cats but the obtained result was not analyzed. In addition, according to the present inventors' analysis, the said data (-2 ± 0.8 mmHg, n=6) was not significant by Student's t-test indicating that PGD_2 was not effective in that experiment. The reason why PGD_2, contrary to the present inventors' finding, raised IOP or was ineffective on IOP in the experiments of the previous workers is not sufficiently clear. However, one of the causes may be attributed to the fact that the experimental animals used therein were, in our asumption, normal or lower IOP animals, in view of the present inventions' finding that PGD_2 does not reduce IOP of the normal or lower IOP rabbits. The present inventors, in contrast to the previous workers, used high IOP animals selected from the available rabbits and discovered that PGD_2 has a reducing activity on IOP in such animals. Advantageously, PGD_2 has been found by the present inventors to cause no side effect such as hyperemia and flare which was observed by administrations of PGE_2, $PGF_{2\alpha}$ and $PGF_{2\alpha}$ derivatives. Furthermore, the present inventors also confirmed the above mentioned activity of PGD_2 in human subjects.

In prostaglandins, Vol. 25 (1983) pp. 13-18, some pharmacological properties of 1-(3-cyclohexyl-3α-hydroxypropyl-2,4-dioxoimidazolidine-5α-heptanic acid (BW 245 C) are described. It is reported that this compound reduces arterial pressure in the spontaneously hypertensive rat.

It is the object of the present invention to provide a new use of prostaglandin D_2-active substances which is directed to the manufacture of a medicament for treatment of ocular hypertension and glaucoma.

In a further aspect, the present invention provides a pharmaceutical composition for treating ocular hypertension and glaucoma comprising effective amount of prostaglandin D_2-active substance in association with a pharmaceutically acceptable carrier, diluent or excipient.

The term "treatment" herein is intended to cover all types of control of the disease including prevention, sustention and therapy.

The prostaglandin D_2-active substance to be used in the present invention includes prostaglandin D_2 and its derivatives. They include the following compounds:

prostaglandin D_2 C_1-C_5 alkyl ester, 1-(3-cyclohexyl-3α-hydroxypropyl)-2,4-dioxoimidazolidine-5α-heptanoic acid, and pharmaceutically acceptable salts thereof.

The compounds having the groups other than them can be prepared in a similar manner to the process for preparing the above known compounds (Adv. PG. TX. LT. Res., 15, 295 and 299, 1985).

The novel compounds can be prepared, for example, by reacting alcohols, amines, or reactive derivatives at their hydroxyl group or amino group with the corresponding free carboxylic acid or its reactive derivative. Examples of the reactive derivative in the above carboxyl group are acid halides, acid anhydrides, activated esters, and activated amides. Among the acid halides, acid chlorides are frequently used. Acid anhydrides include symetric anhydrides and mixed anhydrides. The latter includes, for example,

dialkyl phosphate mixed anhydrides,dialkyl phosphite mixed anhydrides,alkyl carbonate mixed anhydrides and aliphatic carboxylic acid (e.g., pivalic acid, trichloroacetic acid) mixed anhydrides.

As the activated esters, methyl ester, ethyl ester, cyanomethyl ester, p-nitrophenyl ester or N-hydroxysuccinimide may be used. As the activated amides, amides with imidazole, dimethyl imidazole, and triazole may be used. The reactive derivatives in the above hydroxyl group include halides and sulfonic acid (e.g., methanesulfonic acid, toluenesulfonic acid) esters.

As the reactive derivative in the above amino group, there may be used the Schiff bases with aldehydes (e.g., acetaldehyde, isopentanal, benzaldehyde), reaction products with silyl compounds (e.g., trimethylsilyl chloride, trimethylsilyl acetamide) or reaction products with phosphoric compounds (e.g., phosphorus trichloride, phosphorus oxychloride). When a free carboxylic acid is used, the reaction is advantageously effected in the presence of a condensing agent. Examples of the condensing agent are N,N'-dicyclohexyl-carbodiimide, N-cyclohexyl-N'-morphorinoethyl carbodiimide, N,N'-diisopropyl carbodiimide, N-ethylbenzisoxasolium salt, 2-chloro-1-methyl pyridinium salt, N,N'-carbonyl diimidazole, phosphorus trichloride and phosphorus oxychloride. The reaction is usually carried out in a solvent. The solvent includes dioxane, methylene chloride, tetrahydrofuran, dimethylformamide, pyridine, benzene, toluene and xylene.

A preferred method of preparation is shown, as follows:-

To a dry acetone solution (2 ml) containing prostaglandin D_2 (10 mg) kept at -10 °C under nitrogen stream are added triethylamine (10 mg) and isobutyl chloroformate (7.6 mg), followed by addition of an acetone solution containing an excess amount of alcohol or amine, and the mixture is stirred overnight at room temperature. The solvent is distilled off, and the residue is purified for example by chromatography.

The dosage of the above prostaglandin D_2-active substance is usually 0.01 to 100 mg/kg, which is administered by such routes as topical, oral, intrarectal, intraocular, intravascular, etc. For administration, the active ingredient may be mixed with pharmaceutical carriers such as organic or inorganic, solid or liquid vehicles suitable for particular administration route such as topical, oral, intrarectal, intraocular, intravascular, etc. and administered in the form of a conventional pharmaceutial preparation. Such preparation includes solids such as tablets, granules, powders, capsules, and liquids such as solutions, suspensions and emulsions. The above carrier includes starch, lactose, glucose, sucrose, dextrin, cellulose, paraffin, fatty acid glyceride, water and alcohol. If necessary, auxiliaries, stabilizers, wetting agents, emulsifiers, lubricants, binders, and other conventional additives may be added.

The prostaglandin D_2-active substance has an advantage that it remarkably reduces IOP without being accompanied with any transient rise in IOP in wide range of dosage. Accordingly, the prostaglandin D_2-active substance is useful for treatment or alleviation of glaucoma. Also, the prostaglandin D_2-active substance has an advantage that it exhibit the IOP reducing action in case of high IOP and not in case of lower than normal value. Accordingly, the prostaglandin D_2-active substance gives no side effect even when used for prevention of glaucoma. In these respect, the prostaglandin D_2-active substance has excellent advantages which have not seen in the conventional drugs.

The present invention is now illustrated in further detail by way of the following Examples.

Formulation Example 1

(a) Prostaglandin D_2	10 mg
(b) Phosphate buffer (pH 7.3)	10 ml

The above (a) and (b) are filled in the separate vials. At the time of use, they are dissolved together to make an ophthalmic solution or injection.

Formulation Example 2

(a) Prostaglandin D_2	10 mg
(b) Sesame oil	10 ul

The above (a) and (b) are filled in the separate vials. At the time of use, they are dissolved together.

Formulation Example 3

Prostaglandin D_2	50 mg
Lactose	245 mg
Magnesium stearate	5 mg

The above compounds are mixed according to conventional procedure, granulated, and filled in a gelatine hard capsules.

Prostaglandin D_2 in the above Formulation may be replaced by other PGD_2-active ingredient.

Example 1

Albino rabbits (female, 1.5 - 3.5 kg) were restrained in metal rabbit holders and IOP was measured with an applanation pneumatonograph (made by Alcon). Prior to measurement of IOP, Benoxil 0.4 % solution (oxybuprocaine hydrochloride 0.4 % solution, made by Santen Seiyaku) was instilled to effect surface anaesthetization. Subsequently, a buffer containing a test substance was administered topically to one eye and a buffer only to the other eye which serves as a control.

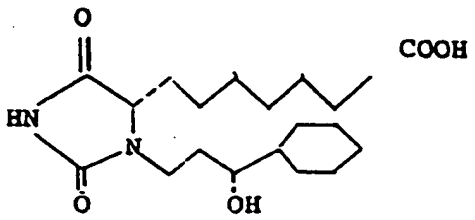
As the test substance, prostaglandin D_2 (50 ug) was used, which was administered as a solution in a phosphate buffer of pH 7.3 (50 ul). The experiments were repeated 9 times, and the average value thereof was adopted.

The results in the case where rabbits showed an initial IOP of 19.2 ± 1.32 mm Hg are showed in Fig. 1. It can be seen from Fig. 1 that the IOP showed a remarkable reduction at 30 minutes after the administration of prostaglandin D_2 (shown as PGD_2 in the drawing) which lasted to at least 7 hours later. The IOP recovered approximately the original value after 20 to 24 hours.

The results in the case where rabbits showed an initial IOP of 13 ± 0.71 mm Hg are shown in Fig. 2. It can be seen from Fig. 2 that prostaglandin D_2 did not exhibit the effect to the rabbits having low IOP (It is to be noted that since the above IOP measuring device is one for human use, the reading of the IOP value does not necessarily agree with the absolute IOP value of rabbit). The test results are shown by using ΔIOP = IOP exp (intraocular pressure of the eyes to which test substance was administered) - IOP cont (intraocular pressure of control eyes).

Example 2

The test procedure of Example 1 was repeated except that 1-(3-cyclohexyl-3α-hydroxypropyl)-2,4-dioxoimidazolidine-5α-heptanic acid of the following formula:



(abbrev. BW245C) was used in place of prostaglandin D_2. The results are shown in Fig. 3. From Fig. 3 it can be seen that, on administration of BW245C to a high IOP rabbit, remarkable IOP reduction is shown at 30 minutes after administration as in prostaglandin D_2.

Example 3

The test procedure of Example 1 was substantially repeated using 16,16-dimethylprostaglandin D_2 - (abbrev., 16,16-Me_2 PGD_2) as a test substance in place of prostaglandin D_2. However, as this compound is hardly soluble in water, it was administered in the form of a solution in olive oil (for 50 ug instillation). To the

control eye, the same amount of olive oil was administered. The initial IOP of rabbits (n = 3) was 29.0 ± 3.9 mm Hg. The results are shown in Fig. 4. It can be seen from Fig. 4 that 16,16-Me_2 PGD_2 also shows remarkable IOP reduction at 30 minutes after the administration. In this case, however, the sustaining time was slightly shorter.

Example 4

The test procedure of Example 1 was substantially repeated using prostaglandin D_2 methyl ester as a test substance in place of prostaglandin D_2. However, as this compound is hardly soluble in water, it was administered in the form of a solution in olive oil (for 50 ug instillation). To the control eye, the same amount of olive oil was administered. The initial IOP of rabbits (n = 4) was 19.3 ± 1.1 mm Hg. The results are shown in Fig. 5. It can be seen from Fig. 5 that PGD_2 methyl ester also shows remarkable IOP reduction at 30 minutes after the administration.

Example 5

The test procedure of Example 1 was substantially repeated using a human subject in place of rabits. The dose of PGD_2 was 5μg. The initial IOP was 18.0. The results are shown in Fig. 6. It can be seen from Fig. 6 that PGD_2 shows remarkable IOP reduction in human.

Example 6

Albino rabbits weighing 2-2.5kg were restrained in rabbit holders. PGD_2 was dissolved in 100mM potassium phosphate (pH 7.3) and administered topically on one eye. The other eye received the vehicle alone. IOP values were measured for various doses as in Example 1. The results are shown in Fig. 7. From Fig. 7, it can be seen that PGD_2 is effective at doses of 2 μg and more.

Example 7

The test procedure of Example 6, various test compounds were administered at 50μg dose. Hyperemia and flare were monitored by slit-lamp examination. Irritatory response was defined by the lid-closing. The results are shown in the following Table in which all scores are shown in four grades (-, ±, +, + +) as an average of at least 4 animals during four-hour observation.
The symbols have the following meaning:

- \- stands for a negative or absent effect
- ± stands for a boundary effect
- \+ stands for a positive effect and
- \+ + stands for a strongly positive effect.

Compound	Irritation	Hyperemia		Flare
		conjunctiva	iris	
PGD_2	-	-	-	-
PGE_2	+ +	+ +	+ +	+
$PGF_{2\alpha}$	+ +	+ +	+ +	±

It can be seen from the above results that PGD_2 has no irritation, hyperemia and flare at a dose which is toxic by PGE_2 and $PGF_{2\alpha}$.

Example 8

In the test procedure of Example 7, PGD_2 (50μg), PGE_2 (2μg) and $PGF_{2\alpha}$ (10μg) were administered as the test compounds. Aqueous humor was carefully withdrawn from the eye by a needle under a binocular microscope and protein content was determined using bovine serum albumin as a standard. The results are shown in Fig. 8. From Fig. 8, it can be seen that protein content does not significantly change after administration of PGD_2 while it increase after administration of PGE_2 or $PGF_{2\alpha}$.

In Figs. 7 and 8, statistical significance was determined by paired t-test and Duncan's multiple range test, respectively. *... P<0.05, **... P<0.01.

In Fig. 8, open circles designate PGE_2 (2μg), closed circles PGD_2 (50μg) and closed triangles $PGF_{2\alpha}$ - (10μg).

Claims

1. Use of a prostaglandin D_2-active substance selected from prostaglandin D_2, prostaglandin D_2 C_1-C_5 alkyl ester, 1-(3-cyclohexyl-3α-hydroxypropyl)-2,4-dioxoimidazolidine-5α-heptanoic acid, and pharmaceutically acceptable salts thereof for the manufacture of a medicament for topical treatment of ocular hypertension and glaucoma wherein the concentration of said prostaglandin D_2-active substance is such that it is administered at a dosage of about 2 to 50μg/eye.

2. The use according to claim 1, in which the said compound is prostaglandin D_2 or a pharmaceutically acceptable salt or ester thereof.

3. The use according to claim 1, in which the said compound is 1-(3-cyclohexyl-3α-hydroxypropyl)-2,4-dioxoimidazolidine-5α-heptanoic acid.

4. The use according to claim 1, in which the said prostaglandin D_2-active substance is formulated in the form of a solid coupled with a solvent system for dissolving the said solid.

5. The use according to claim 4, in which the solvent system comprises mainly water or vegetable oil.

Patentansprüche

1. Verwendung eines Prostaglandin D_2-Wirkstoffs, ausgewählt aus Prostaglandin D_2, Prostaglandin D_2-C_1-C_5-Alkylester, 1-(3-Cyclohexyl-3α-hydroxypropyl)-2,4-dioxoimidazolidin-5α-heptansäure und pharmazeutisch verträglichen Salzen davon, für die Herstellung eines Medikaments zur lokalen Behandlung von Augenhochdruck und Glaukom, wobei die Konzentration des Prostaglandin D_2-Wirkstoffs so ist, daß er mit einer Dosierung von etwa 2 bis 50 μg/Auge verabreicht wird.

2. Verwendung nach Anspruch 1, wobei die Verbindung Prostaglandin D_2 oder ein pharmazeutisch verträgliches Salz oder Ester davon ist.

3. Verwendung nach Anspruch 1, wobei die Verbindung 1-(3-Cyclohexyl-3α-hydroxypropyl)-2,4-dioxoimidazolidin-5α-heptansäure ist.

4. Verwendung nach Anspruch 1, wobei der Prostaglandin D_2-Wirkstoff in Form eines Feststoffs zusammen mit einem Lösungsmittelsystem zum Auflösen des Feststoffs formuliert ist.

5. Verbindung nach Anspruch 4, wobei das Lösungsmittelsystem hauptsächlich Wasser oder ein pflanzliches Öl umfaßt.

Revendications

1. Utilisation d'une substance présentant l'activité de la prostaglandine D_2, choisie parmi la prostaglandine D_2, un alkylester en C_1-C_5 de la prostaglandine D_2, l'acide 1-(3-cyclohexyl-3α-hydroxypropyl)-2,4-dioxoimidazolidine-5α-heptanoïque et ses sels pharmaceutiquement acceptables, pour la fabrication d'un médicament pour le traitement topique de l'hypertension oculaire et du glaucome, dans laquelle la concentration de ladite substance présentant l'activité de la prostaglandine D_2 est telle qu'elle est administrée à une dose d'environ 2 à 50 μg/oeil.

2. Utilisation selon la revendication 1, dans laquelle ledit composé est la prostaglandine D_2 ou l'un de ses sels ou esters pharmaceutiquement acceptables.

3. Utilisation selon la revendication 1, dans laquelle ledit composé est l'acide 1-(3-cyclohexyl-3α-hydroxypropyl)-2,4-dioxoimidazolidine-5α-heptanoïque.

4. Utilisation selon la revendication 1, dans laquelle ladite substance présentant l'activité de la prostaglandine D_2 est formulée sous forme d'un solide couplé à un système solvant pour dissoudre ledit solide.

5. Utilisation selon la revendication 4, dans laquelle le système solvant comprend principalement de l'eau ou une huile végétale.

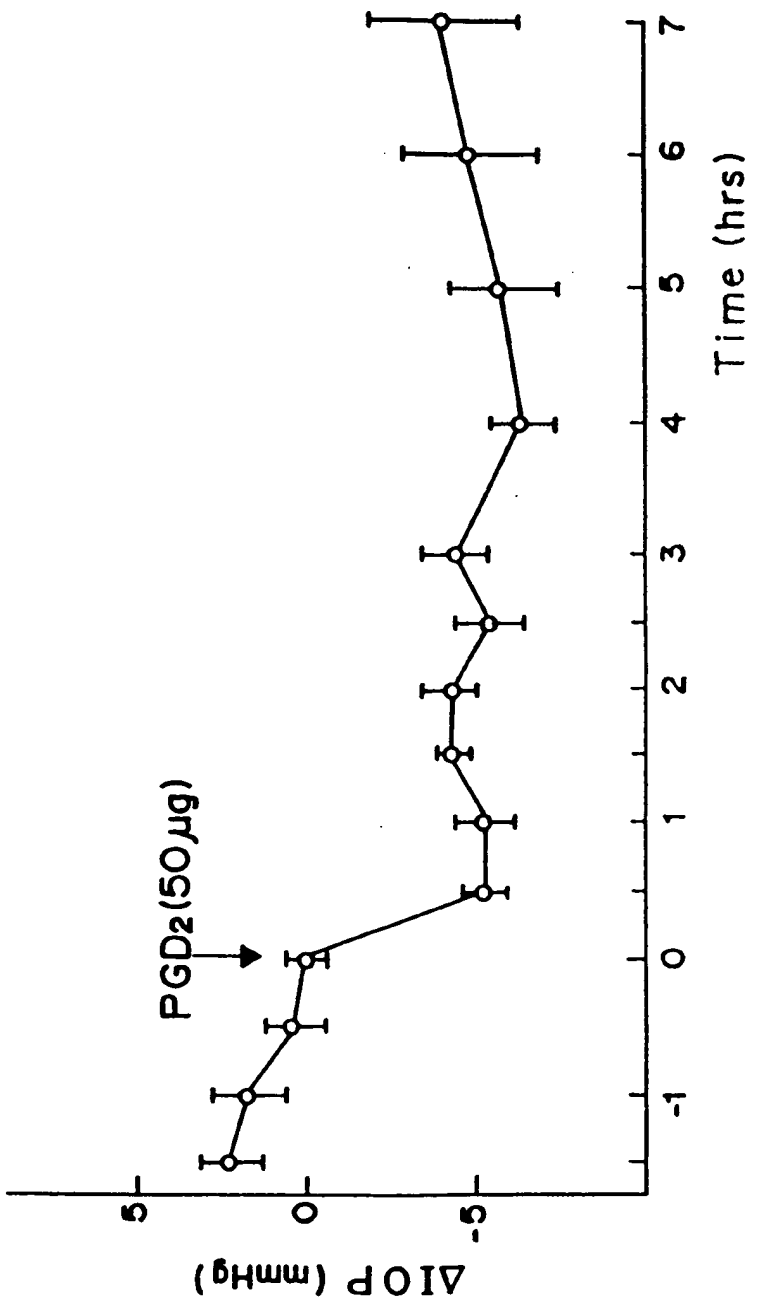


Fig. 1

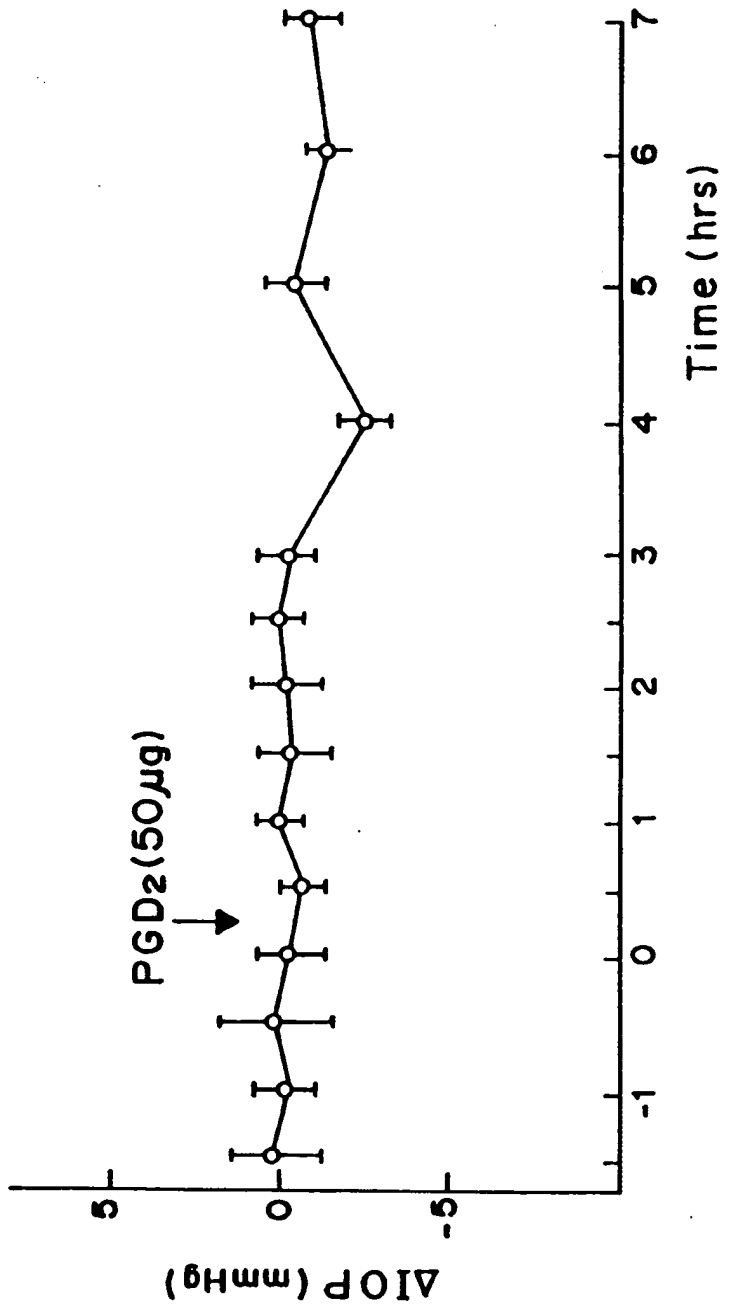


Fig. 2

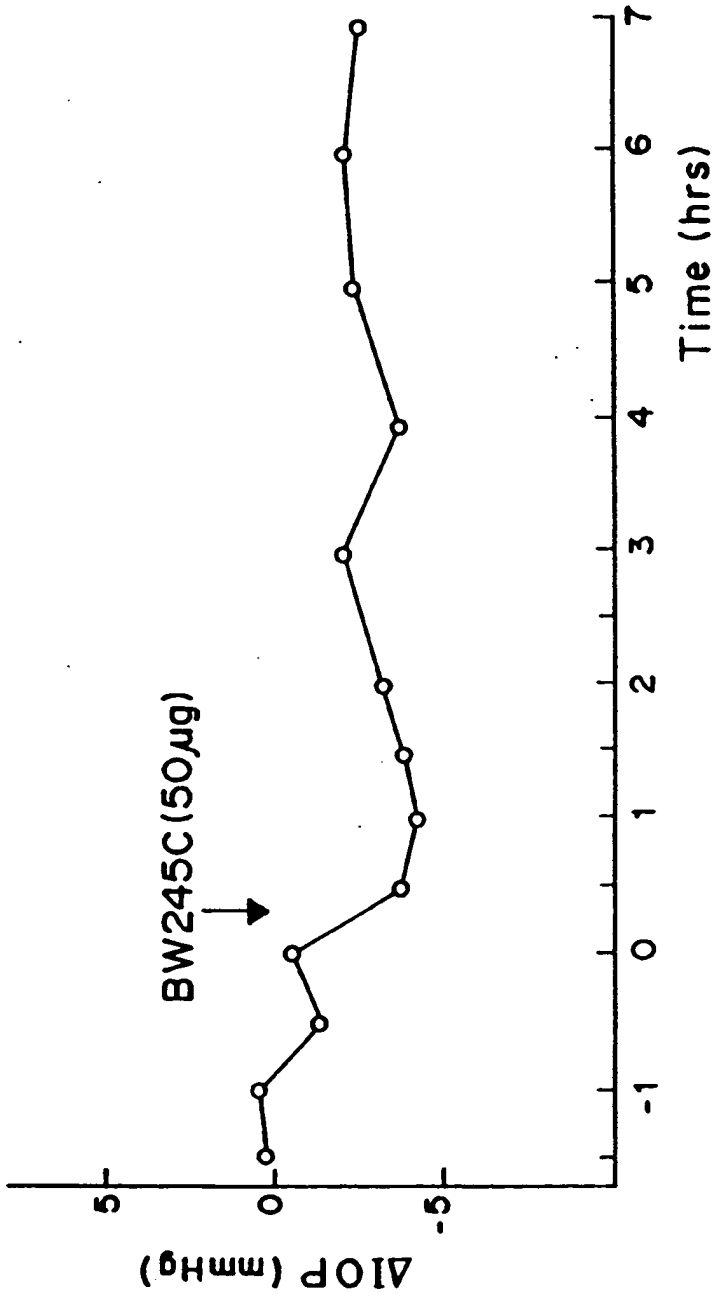


Fig. 3

Fig. 4

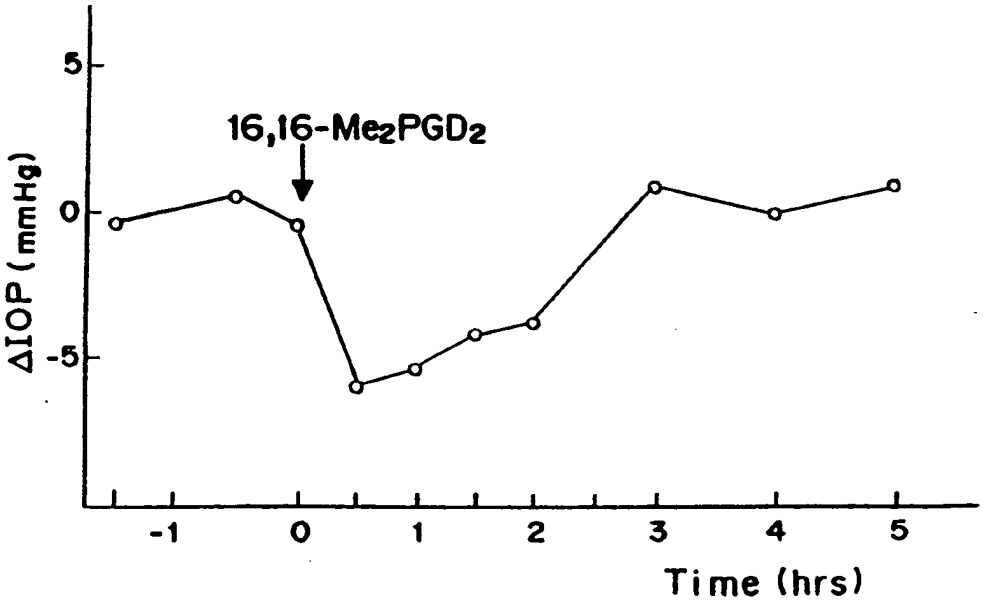

16,16-Me2PGD2
ΔIOP (mmHg)
5
0
-5
-1
0
1
2
3
4
5
Time (hrs)

Fig. 5

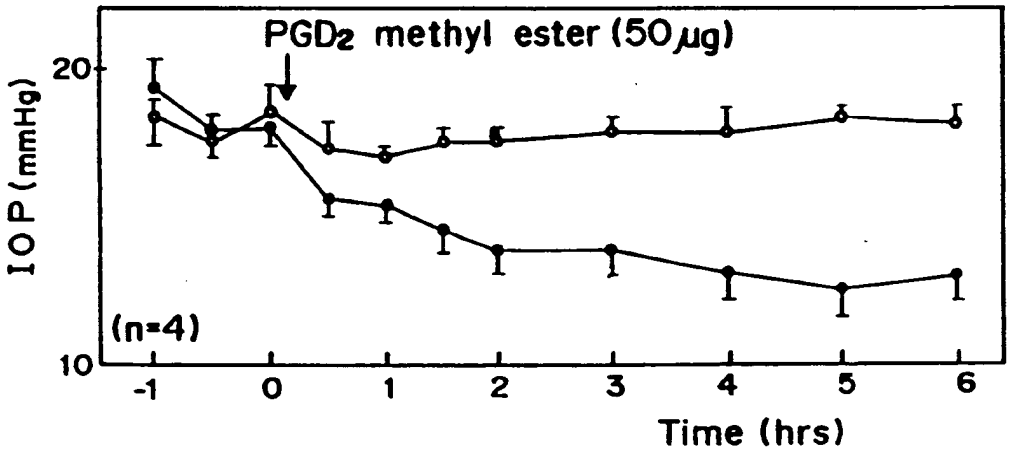

PGD2 methyl ester (50μg)
IOP (mmHg)
20
10
(n=4)
-1
0
1
2
3
4
5
6
Time (hrs)

Fig. 6

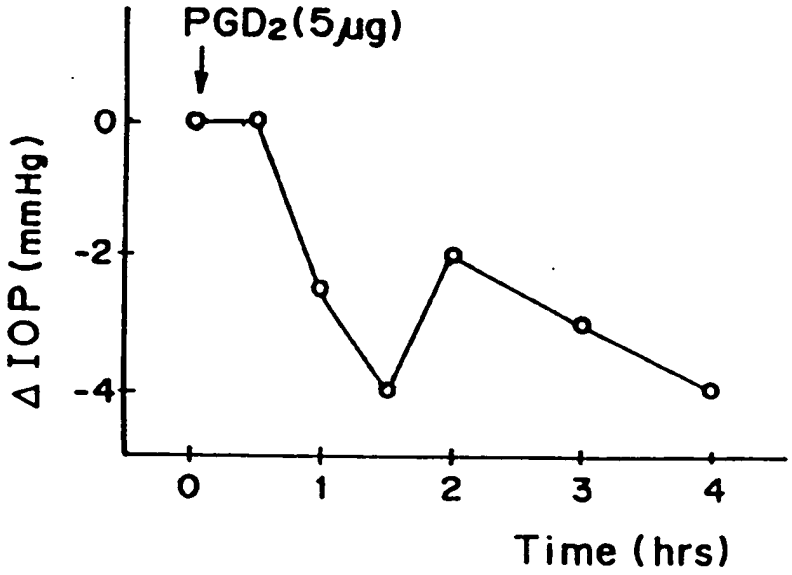

PGD2(5μg)
0
-2
-4
Δ IOP (mmHg)
0
1
2
3
4
Time (hrs)

Fig. 8

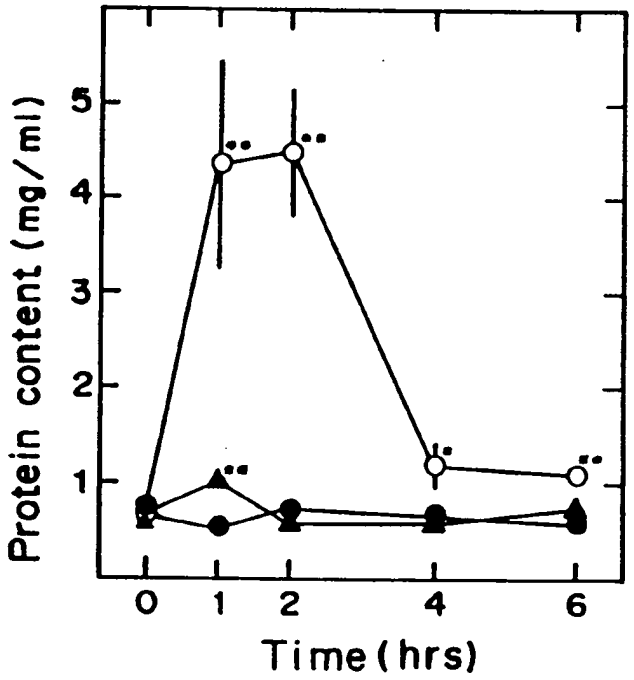
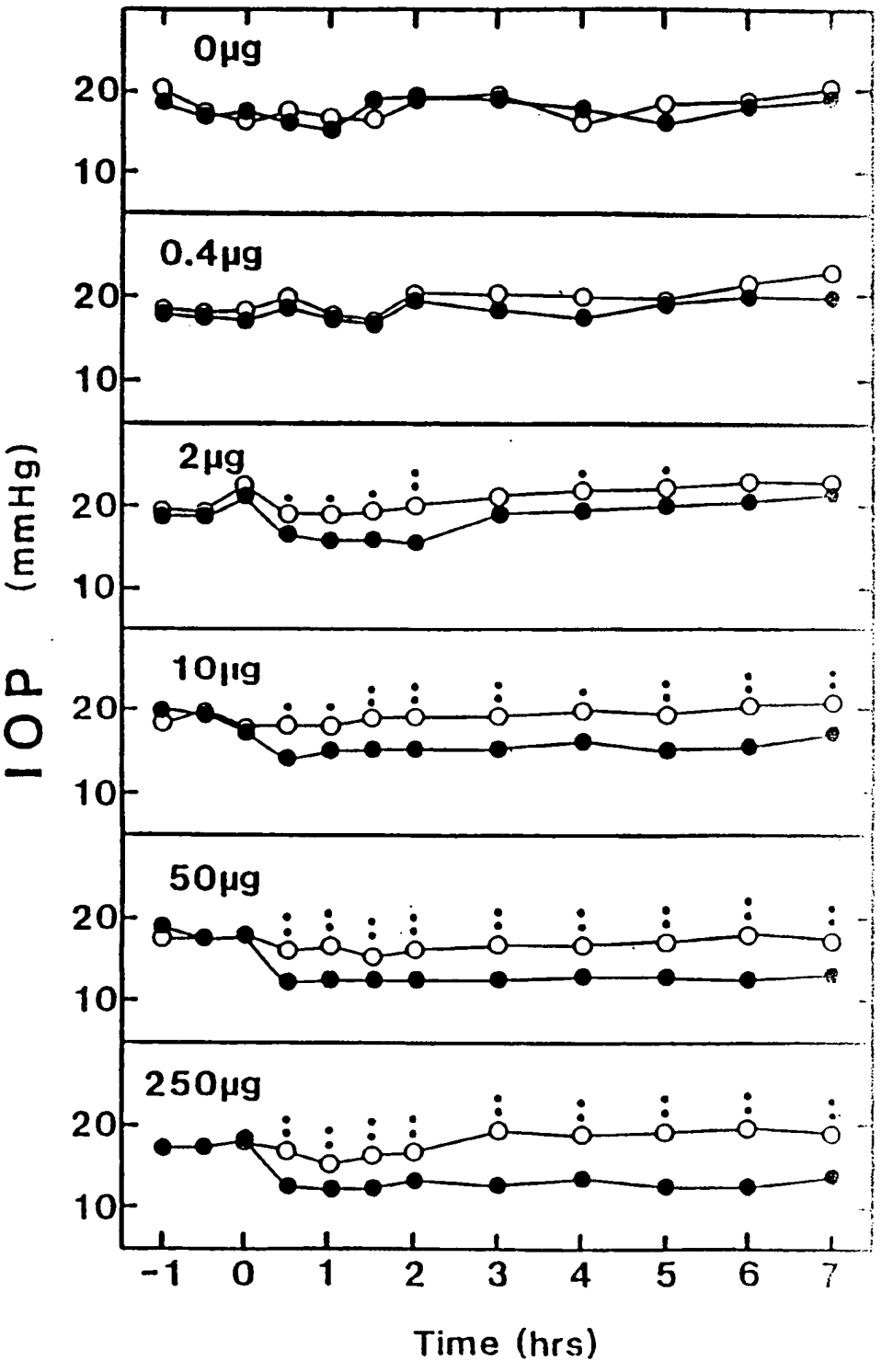

Protein content (mg/ml)
5
4
3
2
1
0
1
2
4
6
Time (hrs)

Fig. 7


0μg
0.4μg
2μg
10μg
50μg
250μg
20
10
IOP (mmHg)
-1
0
1
2
3
4
5
6
7
Time (hrs)